REMARKS

Prior to entry of this amendment, claims 1-17 were pending in the application. Claims 1, 2, 6 and 8-17 have been amended and new claims 36-38 are submitted herein. Claims 3-5 and 7 have been canceled. Applicants expressly reserve the right to pursue protection of any or all of the canceled subject matter in one or more continuing applications. After entry of this amendment, **claims 1, 2, 6, 8-17 and 36-38 will be pending in this application**.

Support for the amendments and new claims can be found throughout the specification and claims as originally filed. Claims 1, 2, 6 and 8-17 are amended to specify that the polypeptide is "isolated," support for which can be found, for example, on page 2, lines 9-11; page 8, lines 30-36; and page 16, lines 1-3 of the specification. Claim 1 is further amended to provide a reference sequence for the wild-type constitutively active nuclear orphan receptor (CAR); eliminate reference to a polypeptide "encoding;" replace "native" with "wild-type;" recite that the polypeptide comprises "one or more mutations;" and generally clarify the identity of the claimed CAR polypeptide. Support for the reference sequence, GenBank Accession No. Z30425, can be found in Example 1, beginning on page 18 of the specification. Support for "wild-type" can be found, for example, on page 6, lines 24-30 and page 25, lines 30-32, of the specification. Basis for "one or more mutations" can be found, for example, at page 1, lines 8-10, and page 2, lines 19-28 and 31-38, of the specification.

Claim 2 is amended to clarify that the polypeptide comprises "one or more mutations" and to insert the reference sequence GenBank Accession No. Z30425. Claim 6 is amended to correct claim dependency, specify the polypeptide comprises "one" mutation and insert reference to GenBank Accession No. Z30425. Claim 8 is amended to correct claim dependency. Claim 9 is amended to clarify that the constitutive activity of the polypeptide is altered, support for which can be found, for example, on page 19, lines 20-25 and page 20, lines 21-26 of the specification. Claims 10 and 13 are amended to clarify that the polypeptide "induces" activity, basis for which can found in the specification, for example on page 2, lines 31-38 and page 6, lines 18-23. Claim 15 is amended to recite that the isolated polypeptide is "at least 70% pure," support for which can be found on page 10, lines 6-13 of the specification. Claim 16 is amended to insert "CAR-responsive" to clarify the relationship between the two components of the claimed kit. Support

for "CAR-responsive" can be found throughout the specification, such as at page 2, lines 15-18; page 3, lines 18-30; page 6, lines 18-23 and 31-38; and page 7, lines 1-14.

The specification is amended to include the deposit dates of GenBank Accession No. Z30425 (human CAR) and GenBank Accession No. AF009327 (murine CAR).

No new matter has been added by these amendments, and no amendments are made to distinguish prior art.

No new matter is introduced by inclusion of GenBank Accession Nos. in the claims and providing deposit dates to the specification, as the specification as filed included the GenBank Accession Nos. In addition, the GenBank deposit dates are prior to the priority date of the present application. Thus, the sequence corresponding to the GenBank Accession Nos. cited in the specification were publicly available prior to the priority date of the present application, and it is clear to one skilled in the art which sequence was referenced by citation to a GenBank Accession No.

INFORMATION DISCLOSURE STATEMENT

The Office indicates the information disclosure statement filed August 18, 2004 does not comply with 37 C.F.R. §1.97 and 1.98. Specifically, item AG (Accession No. Z30425) was not considered because the database from which the referenced sequence was obtained has not been identified and the date of deposit was not provided. In response, Applicants submit a supplemental information disclosure statement indicating that Accession No. Z30425 was deposited with GenBank on March 8, 1994. Applicants submit the information disclosure statement is in compliance with 37 C.F.R. §1.97 and 1.98.

REJECTION UNDER 35 U.S.C. §101

Claims 1-14 are rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. The Office states that the polypeptide of claim 1 is not sufficiently distinguishable over a naturally occurring mutated polypeptide. As suggested by the Examiner, claims 1, 2, 6 and 8-17 are amended herein to recite that the polypeptide is an "isolated

polypeptide." Claims 3-5 and 7 are canceled herein, rendering the rejection moot as it pertains to these claims. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §101.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-17 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants traverse the rejection for the reasons set forth below.

Claim 1 is rejected because the Office indicates (i) it is not clear how a polypeptide could encode another polypeptide; (ii) it is unclear how a non-constitutively active receptor can be made less constitutively active; (iii) the term "native" is unclear; and (iv) using the term "CAR" is not sufficient to distinctly identify the claimed polypeptide. For clarity, claim 1 is amended herein to (i) remove the phrase "polypeptide encoding;" (ii) clarify that the claimed polypeptide is less constitutively active than a wild-type CAR polypeptide; (iii) replace "native" with "wild-type;" and (iv) provide a reference sequence for the CAR polypeptide to clearly identify the claimed polypeptide. Therefore, Applicants submit claim 1 as recited herein is not indefinite.

Claims 1 and 9 are rejected for the recitation of "less constitutively active" and "substantially decrease the non-constitutive activity," respectively. The Office argues it is not clear how a receptor can be "more" or "less" constitutively active. Applicants disagree with this statement. The specification clearly defines constitutively active and non-constitutively active receptors and the parameters for determining whether a receptor is "more" or "less" constitutively active. For example, at page 7 of the specification, a less constitutively active CAR (also called a non-constitutively active CAR or non-CAR) is defined as a CAR "that retains the ability to be induced by CAR-responsive xenochemicals and steroids," which includes any CAR "that is not substantially constitutively active *in vitro*, such that the receptor has sufficiently low activity that its induction by a CAR-responsive steroid and/or xenochemical can be detected *in vitro* when performing a cell-based transfection assay as described in EXAMPLE 1." The specification further states the activity can be 50% less, 25% less, 10% less, 5% less, 2% less or 0% active. Example 1, beginning on page 18 of the specification, describes non-CAR polypeptides and an assay to demonstrate a reduction in their constitutive activity. Although Applicants disagree with the Office's assertion, claim 1 is amended herein to clarify that the claimed polypeptide is less constitutively active than a wild-type constitutively active nuclear orphan receptor. In addition, claim 9 is amended for clarity to recite that the amino acid

substitutions do not "substantially alter the constitutive activity of the polypeptide." Accordingly, Applicants submit claims 1 and 9 are not indefinite.

Claims 2-8 are rejected as allegedly being vague and indefinite for reciting amino acid positions without presenting a reference sequence. Claims 3-5 and 7 are canceled herein, rendering the rejection moot as it pertains to these claims. Claim 1 is amended herein to specify that the amino acid reference sequence is GenBank Accession No. Z30425 and the specification is amended to indicate the sequence was deposited March 8, 1994. Claims 2 and 6 also are amended to insert reference to GenBank Accession No. Z30425. Thus, Applicants submit it is now clear that the amino acid positions recited in claims 2 and 6 refer to the reference sequence of GenBank Accession No. Z30425.

Claims 2, 4 and 6 are rejected as allegedly being unclear how "the mutation" could be at more than one position. Claim 4 is canceled herein rendering the rejection moot as it pertains to this claim. Claim 1 is amended herein to clarify that the polypeptide comprises one or more mutations. In addition, claim 2 is amended to recite "the one or more mutations" correspond to positions Leu342 *and* Leu343 and claim 6 is amended to recite "the one mutation" corresponds to position Leu342 *or* Leu343.

Claims 10 and 13 are rejected for the recitation of "confers." For clarity, claims 10 and 13 are amended to state that the polypeptide "induces" the recited activities.

Claim 16 is rejected as being indefinite for not stating the interrelationship of the items of the claimed kit. In response, claim 16 is amended herein to indicate the steroid and/or xenochemical are "CAR-responsive." Thus, the kit comprises a CAR polypeptide and a CAR-responsive steroid and/or xenochemical. Applicants submit it is clear how the two components of the claimed kit are related.

Based on the amendments and arguments presented above, Applicants submit claims 1-17 are clear and definite. Accordingly, Applicants request withdrawal of each of the rejections under 35 U.S.C. §112, second paragraph.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Office argues that because of the lack of a reference sequence provided for CAR, one of skill in the art "would be unable to predict that producing mutations at the indicated

amino acid residues would result in a protein with the functional characteristics of the protein" as claimed. Furthermore, the Office indicates that the term CAR is used to identify proteins having different functions. Therefore, the Office concludes undue experimentation would be required to make or use the claimed polypeptides. Applicants traverse this rejection.

As discussed above, claim 1 is amended herein to provide a reference sequence (GenBank Accession No. Z30425) for wild-type CAR and the specification is amended to insert the deposit date for the reference sequence. Thus, it is clear that the claimed polypeptide comprises one or more mutations relative to the wild-type CAR polypeptide of GenBank Accession No. Z30425, such that the one or more mutations render the claimed polypeptide less constitutively active than the wild-type CAR polypeptide. With the provided reference sequence, it is clear to one of skill in the art that making mutations at the indicated amino acid residues (for example, the amino acid positions recited in claims 2, 6, 37 and 38) would result in a polypeptide having less constitutive activity than the wild-type CAR polypeptide. The reference sequence also eliminates any ambiguity arising from the term "CAR."

Therefore, Applicants submit claims 1-17 and new claims 36-38 are fully enabled. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 1 and 9-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. The Office argues that the specification describes CAR sequences as including full-length wild-type sequences as well as variants, fragments, homologs and CAR sequences having a specified percent identity to a wild-type CAR, however, no wild-type CAR sequences are definitively recited and the exemplary GenBank sequences listed in the specification do not provide a clear identification of the sequence because deposit dates are not provided. The Office concludes the claims do not meet the written description provision because no specific reference sequence is unambiguously identified. Applicants traverse this rejection.

As discussed above, claim 1 is amended to provide a reference sequence for wild-type CAR (GenBank Accession No. Z30425) and the specification is amended to include the deposit date for GenBank Accession No. Z30425. As recited herein, the amino acid sequence of the claimed polypeptide comprises a wild-type CAR polypeptide sequence of GenBank Accession No. Z30425 comprising one or more mutations that render the claimed polypeptide less

constitutively active than the wild-type CAR polypeptide. Thus, Applicants submit the claims provide an unambiguous identification of the claimed polypeptide and the polypeptides are not defined by functional parameters.

Applicants submit the specification provides a more than adequate written description for claims 1 and 9-17, and new claims 36-38. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

REJECTIONS UNDER 35 U.S.C. §102

Claims 1-3, 6, 8-14 and 17 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Tomko *et al.* (*Proc. Natl. Acad. Sci. U.S.A. 94*:3352-3356, 1997). The Office states that Tomko *et al.* teach the sequence of a CAR receptor, wherein the receptor comprises mutations. The Office concludes that without a reference sequence provided in the claims, Tomko *et al.* meets the limitations of the rejected claims. Applicants traverse this rejection.

Tomko *et al.* describe a sequence for the coxsackievirus and adenovirus receptor, not for a constitutively active nuclear orphan receptor. Alignment of the sequence taught by Tomko *et al.* and the wild-type CAR receptor reference sequence provided in the instant specification and claims, reveals the sequences are highly divergent and have no sequence homology. Tomko *et al.* do not teach each and every limitation of the pending claims, including new claims 36-38, thus the claims are not anticipated. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §102(b).

Claims 1, 10-14 and 17 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Kawamoto *et al.* (*Mol. Endoc. 14*:1897-1905, 2000). The Office alleges Kawamoto *et al.* teach a CAR which has the ability to transactivate the NR1 response element of the CYP2B gene in the presence of estradiol and TCPOBOP. Kawamoto *et al.* do not identify the receptor as a mutated receptor; however, the Office concludes that without a reference sequence provided in the claims, one would not be able to determine what a mutated receptor comprises. Applicants traverse this rejection.

As recited herein, claim 1 specifies the claimed polypeptide comprises one or more mutations relative to the wild-type CAR polypeptide of GenBank Accession No. Z30425. Thus, the claims do provide a reference sequence and one would be able to determine what a mutated

receptor comprises. Furthermore, in contrast to the teachings of the Kawamoto *et al.* reference, which teaches a murine CAR, the pending claims are directed to human CAR. Since Kawamoto *et al.* do not teach a mutated CAR polypeptide, and further do not teach a mutated human CAR polypeptide, Kawamoto *et al.* do not teach each and every limitation of the rejected claims or new claims 36-38. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §102(b).

Claims 1, 10-12 and 15-17 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Tzammell *et al.* (*Mol. Cell Biol. 20:*2951-2958, 2000). The Office alleges Tzammell *et al.* teach a nuclear receptor (CAR) having the ability to transactivate the CYP promoter in the presence of TCPOBOP. Tzammell *et al.* do not identify the receptor as a mutated receptor; however, the Office concludes that without a reference sequence provided in the claims, one would not be able to determine what a mutated receptor comprises. Applicants traverse this rejection.

As discussed above in reference to the rejection in view of Kawamoto *et al.*, claim 1 specifies the claimed polypeptide comprises one or more mutations relative to the wild-type CAR polypeptide of GenBank Accession No. Z30425. Thus, the claims do provide a reference sequence and one would be able to determine what a mutated receptor comprises. Furthermore, in contrast to the teachings of the Tzammell *et al.* reference, which teaches a murine CAR, the pending claims are directed to human CAR. Since Tzammell *et al.* do not teach a mutated CAR polypeptide, and further do not teach a mutated human CAR polypeptide, Tzammell *et al.* do not teach each and every limitation of the rejected claims or new claims 36-38. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §102(b).

REQUEST FOR INTERVIEW

Prior to filing the instant Amendment and Response, Applicants representative, Jodi L. Connolly, requested an interview with the Examiner. However, Applicants were not permitted an interview, despite the fact that the pending Office action is non-final. Therefore, if an additional rejection is asserted, or if the present rejections are maintained, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the

present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. Should the Examiner have further questions or comments with respect to examination of this case, it is respectfully requested that the Examiner telephone the undersigned so that further examination of this application can be expedited.

Respectfully submitted,

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